

Appl. No. 09,700,806
Amd. dated November 22, 2004
Reply to Office Action of June 21, 2004

Amendments to the Claims:

This listing of claims will replace all prior versions and listings of claims in the application.

Listing of Claims:

1. (currently amended) A method of treating a nitric oxide (NO) associated disorder in a mammal, wherein the disorder is hypertension, diabetes, thrombosis, angina, atherosclerosis, or heart failure, comprising administering to said mammal an effective amount of ~~vascular endothelial growth factor (VEGF) variant or VEGF receptor agonist, wherein the variant or agonist~~ that exhibits selective binding affinity for a KDR receptor, wherein the agonist comprises a VEGF variant having one or more amino acid substitutions in a loop containing FLT-1 contact residues D63, E64, and E67 and the binding affinity of the agonist for FLT-1 receptor is reduced as compared to the binding affinity of native VEGF for FLT-1 receptor.

2-7. (canceled)

8. (original) The method of claim 1 wherein said mammal is a human.

9. (canceled)

10. (currently amended) The method of claim 1 wherein said effective amount of ~~VEGF variant or VEGF receptor agonist~~ enhances nitric oxide production in said mammal.

11-13. (canceled)

14. (currently amended) A method of stimulating sustained production of endogenous NO in an endothelial cell, comprising exposing the endothelial cell to an effective amount of a VEGF receptor agonist, ~~wherein the agonist is that exhibits selective binding affinity for a KDR receptor[,]~~ and whereby the induces up-regulation of endothelial NO synthase (eNOS) in the endothelial cell is up-regulated, wherein the agonist comprises a VEGF variant having one or more amino acid substitutions in a loop containing FLT-1 contact residues D63, E64, and E67

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and the binding affinity of the agonist for FLT-1 receptor is reduced as compared to the binding affinity of native VEGF for FLT-1 receptor.

15. (currently amended) The method of claim 14, wherein the ~~VEGF receptor agonist is a~~
VEGF variant comprises one or more amino acid substitutions at or between positions 63 to 66
of native VEGF having selective binding affinity for KDR receptor.

16. (withdrawn) The method of claim 15, wherein the VEGF variant comprises one or more
amino acid substitutions at or between positions 17 to 25 of the native VEGF sequence (SEQ ID
NO: 4).

17. (withdrawn) The method of claim 16, wherein in VEGF variant comprises at least the
following amino acid substitutions: M18E, Y21L, Q22R and Y25S.

18. (canceled)

19. (currently amended) The method of claim ~~18~~15, wherein the ~~VEGF variant comprises at~~
~~least the following amino acid~~ substitution(s)[:] comprises D63S, G65M, or L66R.

20. (canceled)

21. (currently amended) The method of claim 1[4] wherein the disorder is hypertension,
angina, thrombosis, heart failure, or atherosclerosis.

22. (new) The method of claim 1, wherein the VEGF variant comprises one or more amino
acid substitutions at or between positions 63 to 66 of native VEGF.

23. (new) The method of claim 22, wherein the amino acid substitution(s) comprises D63S,
G65M, or L66R.

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24. (new) The method of claim 23, wherein the amino acid substitutions comprise D63S, G65M, and L66R.
25. (new) The method of claim 19, wherein the amino acid substitutions comprise D63S, G65M, and L66R.
26. (new) The method of claim 22, wherein the VEGF variant further comprises one or more amino acid substitutions at or between positions 17 to 25 of native VEGF.
27. (new) The method of claim 26, wherein the amino acid substitution(s) comprises one or more of amino acid substitution(s) at positions 18, 21, 22, or 25.
28. (new) The method of claim 26, wherein the amino acid substitution(s) comprises one or more of M18E, Y21L, Q22R, or Y25S.
29. (new) The method of claim 28, wherein the amino acid substitutions comprise M18E, Y21L, Q22R, and Y25S.
30. (new) The method of claim 26, wherein the VEGF variant comprises one of the following combinations of amino acid substitutions:
- (a) M18E, D63S, G65M, and L66R;
 - (b) Y21L, D63S, G65M, and L66R;
 - (c) Q22R, D63S, G65M, and L66R;
 - (d) Y25S, D63S, G65M, and L66R;
 - (e) M18E, Y21L, D63S, G65M, and L66R;
 - (f) M18E, Q22R, D63S, G65M, and L66R;
 - (g) M18E, Y25S, D63S, G65M, and L66R;
 - (h) Y21L, Q22R, D63S, G65M, and L66R;
 - (i) Y21L, Y25S, D63S, G65M, and L66R;
 - (j) Q22R, Y25S, D63S, G65M, and L66R;
 - (k) M18E, Y21L, Q22R, D63S, G65M, and L66R;

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- (l) M18E, Q22R, Y25S, D63S, G65M, and L66R;
- (m) Y21L, Q22R, Y25S, D63S, G65M, and L66R;
- (n) M18E, Y21L, Q22R, Y25S, and D63S;
- (o) M18E, Y21L, Q22R, Y25S, and G65M;
- (p) M18E, Y21L, Q22R, Y25S, and L66R;
- (q) M18E, Y21L, Q22R, Y25S, D63S, and G65M;
- (r) M18E, Y21L, Q22R, Y25S, D63S, and L66R;
- (s) M18E, Y21L, Q22R, Y25S, G65M, and L66R; or
- (t) M18E, Y21L, Q22R, Y25S, D63S, G65M, and L66R.

31. (new) The method of claim 16, wherein the VEGF variant comprises one of the following combinations of amino acid substitutions:

- (a) M18E, D63S, G65M, and L66R;
- (b) Y21L, D63S, G65M, and L66R;
- (c) Q22R, D63S, G65M, and L66R;
- (d) Y25S, D63S, G65M, and L66R;
- (e) M18E, Y21L, D63S, G65M, and L66R;
- (f) M18E, Q22R, D63S, G65M, and L66R;
- (g) M18E, Y25S, D63S, G65M, and L66R;
- (h) Y21L, Q22R, D63S, G65M, and L66R;
- (i) Y21L, Y25S, D63S, G65M, and L66R;
- (j) Q22R, Y25S, D63S, G65M, and L66R;
- (k) M18E, Y21L, Q22R, D63S, G65M, and L66R;
- (l) M18E, Q22R, Y25S, D63S, G65M, and L66R;
- (m) Y21L, Q22R, Y25S, D63S, G65M, and L66R;
- (n) M18E, Y21L, Q22R, Y25S, and D63S;
- (o) M18E, Y21L, Q22R, Y25S, and G65M;
- (p) M18E, Y21L, Q22R, Y25S, and L66R;
- (q) M18E, Y21L, Q22R, Y25S, D63S, and G65M;
- (r) M18E, Y21L, Q22R, Y25S, D63S, and L66R;
- (s) M18E, Y21L, Q22R, Y25S, G65M, and L66R; or

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(t) M18E, Y21L, Q22R, Y25S, D63S, G65M, and L66R.